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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,227	03/24/2006	Julie A. Dixon	5178	4978
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Barbara A. Shimei Director, Patents & Licensing Bayer HealthCare LLC - Pharmaceuticals 555 White Plains Road, Third Floor Tarrytown, NY 10591			EXAMINER BALASUBRAMANIAN, VENKATARAMAN	
			ART UNIT	PAPER NUMBER
			1624	
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			08/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/573,227

Applicant(s)

DIXON ET AL.

Examiner/Venkataraman
Balasubramanian/**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 March 2006.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-11 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 12/18/2007.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

Claims 1-11 are pending.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 12/18/2007, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salts does not reasonably provide enablement for making solvate or solvate of a salt. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to compound of formula I, or a pharmaceutically acceptable salt solvate or solvate of a salt thereof. Specification is not adequately enabled as to how to make solvate of a salt of compounds of formula (I) Specification has no example of solvate of a salt of the instant compounds. Specification on page 10, second paragraph recites solvate or solvate of a salt thereof but there is no enabling of such compounds.

The compound of formula I embrace pyrimidine compounds substituted with various variable groups.

Even a cursory calculation of the number of compounds embraced in the instant formula (I) based on the generic definition of alkyl., aryl heteroaryl, heterocycl, substituted aryl, heteroaryl, arylalkoxy, arylalkylthio etc would result in millions of compounds. This is of course not the accurate number and the true number of compounds would far exceed this number of compounds. Thus, the genus embraced in the claim 1 is too large and there is no teaching of any solvate or solvate of a salt of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate of a salt formation in general. The state of the art is that is not predictable whether solvates or solvate of a salt s will form or what their composition will be. In the language of the physical chemist, a solvate of a salt of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left

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out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvate of a salt s, which means a different solvent or even the moisture of the air that might change the stable region of the solvate of a salt. In the instant case of solvate of a salt a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to solvate of a salt

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvate of a salt s is unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or solvate of a salt s and hence generalizations cannot be made for series of related compounds".

2. **The predictability or lack thereof in the art:**

Hence, the solvate or solvate of a salt as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. The amount of direction or guidance present:

Examples illustrated in the experimental section are limited to making the compounds not related to solvates and solvate of a salt. There is no example of a solvate or solvate of a salt of instant compound. Over 334 compounds were shown in the examples of the specification each of which has come in contact with water and other solvent but there is no showing that instant compounds formed solvates or solvate of a salt. Hence it is clear that merely bring the compound with solvent or water does not result in solvate or solvate of a salt and additional direction or guidance is needed to make them. Specification has no such direction or guidance.

4. The presence or absence of working examples:

There is no working example of any solvate or solvate of a salt formed. The claims are drawn to solvate of a salt, yet the numerous examples presented all failed to produce a solvate or solvate of a salt or even solvate of a salt. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exists; if they did, they would have formed. Hence, there should be showing supporting that solvates and solvate of a salt of these compounds exist and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specification has no support, as noted above, for compounds generically embraced in the claims 1-11 would lead to desired solvate and solvate of a salt of the compound of formula I. As noted above, the genus embraces over million compounds and hence the breadth of the claim is broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate or solvate of a salt of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 10 and 11 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating breast cancer does not reasonably provide enablement for treating any or all hyperproliferative disorder and any or all cancer, as generically embraced in these claims. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope

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with these claims.

The instant method of use claims 10 and 11 are drawn to treating a disease hyperproliferative disorder and treating cancer, by inhibiting cell proliferation in general .

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of cell proliferation by imparting cytotoxicity by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

The scope of the claims involves all of the millions of compounds of claim 1 as well as the thousand of diseases embraced by the terms proliferative disorder and cancer.

Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the *Helicobacter pylori* infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless. Accordingly, treatments for cancer are normally tailored to the particular type of cancer present, as there is no, and there can be no "magic bullet" against cancer generally.

Thus, the scope of claims is extremely broad.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of cell proliferation, based on limited assay, it is claimed that i treating any or all hyperproliferative disorders including any or all cancers in general, for which there is no enabling disclosure. The scope of the claims includes any or all cancer based on the mode of action of the compound of instant claims for which there are no enabling disclosure. In addition, the scope of these claims as recited would include treatment of various cancers such as lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which is not adequately enabled solely based on the activity of the compounds provided in the specification.

Moreover many if not most of diseases such as psoriasis, lung cancer, brain

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cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The instant compounds are disclosed to have receptor tyrosine kinase inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as cell proliferation inhibitor that would be useful for all sorts of proliferative diseases and cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host.

The scope of the invention includes millions of compounds of claim 1 as well as the thousand and thousand of diseases embraced by the terms recited above.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body.

Also see the PTO website

<<[<http://www.uspto.gov/web/offices/pac/dapp/1_pecba.htm#7>](http://www.uspto.gov/web/offices/pac/dapp/1_pecba.htm#7)>>

ENABLEMENT DECISION TREE, Example F, situation 1) which is directed to the scope of cancers.

Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Denny, Expert Opin.Emerg.Drugs, Vol. 9(1), 105-133 (2004), Wood et al., Current Opinion in Pharmacology, 1, 370377, 2001. See also Mass, R. D., Int. J. Radiation Oncology Bio. Phys. Vol. 58(3): 932-940, 2004 and Fabbro et al. Pharmacology & therapeutics 93, 79-98, 2002. Also see Malumbres

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et al., Trends in Biochemical Sciences, 30(11), 630-641, 2005., Lolli et al., Cell Cycle 4 :4, 572-577, 2005., Sherr et al., Genes & Development 18, 2699-2711, 2004., Fischer Cell Cycle 3:6, 742-746, 2004. Note Malumbres indicates CDK2 gene is dispensable and mice without CDK2 are normal. Sherr also states the without he said gene much of the fetal development occurs normally. Also note Fischer states" recent findings, however, suggest that CDK2 may not be the key cell cycle player previously assumed, after all, It has now become clear that CDKs have functions in physiological processes other than coordination of cell cycle progression, particularly regulation of DNA transcription." Thus, cell proliferation by various mode of action is still exploratory and requires further experimentation.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating hyperproliferative disorders/diseases that require inhibition of cell proliferation due to cytotoxicity activity.

2) The state of the prior art: A publication expressed that the protein kinase inhibition effects are unpredictable and are still exploratory. See Denny, Wood, Mass, R. D., and Fabbro et al., Malumbres et al., Sherr et al., Lolli et al., and Fischer et al., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all hyperproliferative disorders including all cancers and the state of the art is that the effects of cell proliferation inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace use of a huge genus of compounds and any or all proliferative diseases and cancers .

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in

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the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/078,681. Although the conflicting claims are not identical, they are not patentably distinct from each other because the genus of compounds with the currently elected subject matter, composition and method of use embraced in the instant claims are also embraced in the genus of compounds, composition and method of use of earlier filed copending application 11/078,681. Thus, it would be obvious to one trained in the art to make compounds of the genus of the copending application and expect these compounds including instant compounds to have use recited therein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

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applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624